Thyroid Cancer Outcomes in Filipino Patients

Lukas H. Kus, MSc; Manish Shah, MD; Spiro Eski, MD; Paul G. Walfish, MD; Jeremy L. Freeman, MD, FRCSC

Objective: To compare the outcomes of patients having thyroid cancer among Filipinos vs non-Filipinos.

Design: Retrospective medical record review.

Setting: High-volume tertiary referral center in Toronto, Ontario, Canada.

Patients: A total of 499 patients with thyroid cancer (36 Filipino and 463 non-Filipino) treated at Mount Sinai Hospital from January 1, 1984, to August 31, 2003, with a minimum 5-year follow-up period and a minimum 1.0-cm tumor size. Patients were identified from a thyroid cancer database. Data on patient, tumor, and treatment factors were collected along with outcomes.

Main Outcome Measures: The presence of thyroid cancer recurrence, the rate of death from disease, and the time to recurrence.

Results: The 2 groups were similar for sex, age, history of head and neck radiation exposure, family history of thyroid cancer, follow-up time, tumor size, tumor pathologic findings, presence of tumor multifocality, stage of primary disease, type of thyroid surgery, use of postoperative radioactive iodine therapy, and use of external beam radiation therapy. Filipino patients experienced a thyroid cancer recurrence rate of 25% compared with 9.5% for non-Filipino patients (odds ratio, 3.20; 95% confidence interval, 1.23-7.49; P=.004). On multivariate analysis, the increased risk of thyroid cancer recurrence persisted for Filipino patients (odds ratio, 6.99; 95% confidence interval, 2.31-21.07; P<.001). No significant differences were noted between Filipino patients and non-Filipino patients regarding the rate of death from disease (5.6% vs 1.9%) and the time to recurrence (52.6 vs 53.1 months).

Conclusions: Filipino patients have a significantly higher risk of thyroid cancer recurrence compared with non-Filipino patients. However, no significant difference was noted in the time to recurrence or the rate of death from disease. These findings justify a more aggressive initial management and follow-up regimen for Filipino patients with thyroid cancer.

analysis, Filipino patients initially seen with thyroid nodules were reported to have an almost 70% rate of thyroid cancer, while the rate was less than 40% for control subjects.19

Given the high prevalence of thyroid cancer among Filipinos, the possibility that this population may also be at greater risk for negative outcomes of thyroid cancer merits further investigation. The objective of this study was to perform a retrospective medical record review to determine whether there is a significant difference between Filipino patients and the general patient population in the rates of thyroid cancer recurrence and death from disease and in the time to recurrence.

METHODS

A retrospective medical record review was performed among patients with thyroid cancer who were seen at Mount Sinai Hospital, a high-volume tertiary referral center in Toronto, Ontario, Canada. Total of 499 patients (36 Filipino and 463 non-Filipino) treated between January 1, 1984, and August 31, 2003, who had a minimum 5-year follow-up period and a minimum 1.0-cm tumor size were identified from the thyroid cancer database maintained by one of us (P.G.W.). This patient cohort represents all thyroid cancer cases referred to another of us (J.L.F.) by the study’s senior endocrinologist (P.G.W.) and is a subset of our overall volume for that period, which amounts to several thousand managed cancers. Patient data collected included sex, age, date of birth, history of head and neck radiation exposure, family history of thyroid cancer, Filipino race/ethnicity, tumor size, presence of tumor multifocality, tumor pathologic findings, stage of primary disease, type of thyroid surgery, date of surgical procedure, date of radioactive iodine therapy, date of external beam radiation therapy, date of recurrence diagnosis, date of death from disease, and date of most recent follow-up visit.

Filipino status was defined as Filipino race/ethnicity and birth in the Philippines, which were documented in the database during a patient’s first clinical visit or by follow-up telephone interview. Stage of primary disease was classified according to the system proposed by DeGroot et al.20: I (intrathyroidal), II (lymph node involvement), III (extrathyroidal spread), or IV (distant metastases). Surgical procedures were classified as subtotal thyroidectomy (lobectomy plus isthmusectomy), total thyroidectomy with any type of neck or mediastinal lymph node dissection.

Disease outcomes were measured by the presence of thyroid cancer recurrence, the time to recurrence, and the rate of death from disease. Thyroid cancer recurrence was defined as any evidence of disease (imaging, thyroglobulin estimation, or biopsy specimen) requiring further therapy (iodine I 131 therapy or surgery) after initial curative treatment and was classified as local (thyroid bed), regional (neck or mediastinal lymph nodes), or distant. The time to recurrence was calculated based on the date of primary surgery and the date of recurrence diagnosis. Patients who were initially seen with distant metastases and who had subsequent evidence of residual disease were not considered to have thyroid cancer recurrence. Patients who died of disease before reaching the minimum 5-year follow-up period were included in the study.

Collected data were tabulated in spreadsheet format using commercially available software (Excel; Microsoft, Redmond, Washington) and were imported into a software program (STATA, version 8.2; StatCorp LP, College Station, Texas) for all statistical analyses. Univariate analysis was performed using the χ² test or t test wherever appropriate. Multivariate analysis was performed using logistic regression, and comparisons for significance were made using likelihood ratio tests. All potential confounding variables were included. However, certain variables were dropped from the analysis because of colinearity. Appropriate sensitivity analyses were performed to ensure that the results were not significantly altered. Finally, time-to-event analysis was performed using standard Kaplan-Meier survival analysis techniques. For all analyses, the significance level was set at 2-sided P < .05.

RESULTS

Our analysis identified 36 Filipino and 463 non-Filipino patients treated for thyroid cancer at Mount Sinai Hospital. Patient, tumor, and treatment characteristics are summarized in Table 1. Univariate analysis confirmed that Filipino patients and non-Filipino patients were similar for sex, follow-up time, history of head and neck radia-
Thyroid cancer recurrence was detected in 9 of 36 Filipino patients (25.0%) and in 44 of 463 non-Filipino patients (9.5%). Univariate analysis revealed that Filipino patients were significantly more likely to develop thyroid cancer recurrence than the control group (odds ratio [OR], 3.20; 95% confidence interval [CI], 1.23-7.49; \( P = .004 \)). On multivariate analysis, when controlled for sex, age group, history of head and neck radiation therapy, family history of thyroid cancer, tumor size, tumor pathologic findings, stage of primary disease, use of radioactive iodine therapy, and type of thyroid surgery, the increased risk of thyroid cancer recurrence persisted for Filipino patients (OR, 6.99; 95% CI, 2.31-21.07; \( P < .001 \)). Almost identical results were obtained when patients with anaplastic, medullary, and insular carcinomas were excluded from the multivariate analysis.

Details of patient, tumor, treatment, and recurrence data for Filipino patients with thyroid cancer recurrence are summarized in Table 2. All patients with recurrent disease initially had well-differentiated thyroid cancer, and most (5 of 9) had early-stage disease. Five patients were initially treated with total thyroidectomy, while 4 patients were initially treated with total thyroidectomy plus any type of neck or mediastinal lymph node dissection. All 9 patients with thyroid cancer recurrence were initially treated with radioactive iodine therapy, and 2 patients with advanced (stage III) disease received adjunct external beam radiation therapy. Most patients (6 of 9) had regional recurrence, while 2 patients had local recurrence. One patient had recurrence with distant metastases to lung and bone.

Regarding the rate of death from disease, 2 of 36 Filipino patients (5.6%) and 9 of 463 non-Filipino patients (1.9%) died of thyroid cancer. Although Filipino patients had a higher rate of death from disease, the difference between the 2 groups was nonsignificant (OR, 2.96; 95% CI, 0.30-15.20; \( P = .16 \)). This difference remained nonsignificant (\( P = .26 \)) on multivariate analysis. The mean times to recurrence were 52.6 months (range, 10-150 months) for Filipino patients and 53.1 months (range, 10-180 months) for non-Filipino patients. This difference in the time to recurrence between the groups was not significant on Kaplan-Meier analysis (\( P = .99 \), log-rank test) (Figure).

**Table 2. Patient, Tumor, and Treatment Characteristics Among Filipino Patients With Thyroid Cancer Recurrence**

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Tumor Pathologic Findings</th>
<th>Tumor Size, cm</th>
<th>Stage of Primary Diseasea</th>
<th>Type of Thyroid Surgery</th>
<th>RAI</th>
<th>EBRT</th>
<th>Thyroid Cancer Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/36</td>
<td>Follicular</td>
<td>4.0</td>
<td>I</td>
<td>Total</td>
<td>Yes</td>
<td>No</td>
<td>Local</td>
</tr>
<tr>
<td>2/F/45</td>
<td>Follicular</td>
<td>1.0</td>
<td>I</td>
<td>Total</td>
<td>Yes</td>
<td>No</td>
<td>Regional</td>
</tr>
<tr>
<td>3/M/45</td>
<td>Papillary</td>
<td>3.5</td>
<td>I</td>
<td>Total</td>
<td>Yes</td>
<td>No</td>
<td>Regional</td>
</tr>
<tr>
<td>4/F/40</td>
<td>Follicular</td>
<td>3.2</td>
<td>I</td>
<td>Total</td>
<td>Yes</td>
<td>No</td>
<td>Regional</td>
</tr>
<tr>
<td>5/F/55</td>
<td>Papillary</td>
<td>2.0</td>
<td>III</td>
<td>Total plus neck</td>
<td>Yes</td>
<td>No</td>
<td>Regional</td>
</tr>
<tr>
<td>6/F/35</td>
<td>Papillary</td>
<td>1.0</td>
<td>II</td>
<td>Total plus neck</td>
<td>Yes</td>
<td>No</td>
<td>Regional</td>
</tr>
<tr>
<td>7/F/40</td>
<td>Papillary</td>
<td>2.0</td>
<td>I</td>
<td>Total plus neck</td>
<td>Yes</td>
<td>No</td>
<td>Regional</td>
</tr>
<tr>
<td>8/F/28</td>
<td>Papillary</td>
<td>2.0</td>
<td>III</td>
<td>Total plus neck</td>
<td>Yes</td>
<td>No</td>
<td>Regional</td>
</tr>
<tr>
<td>9/M/54</td>
<td>Papillary</td>
<td>2.5</td>
<td>III</td>
<td>Total plus neck</td>
<td>Yes</td>
<td>Yes</td>
<td>Distant</td>
</tr>
</tbody>
</table>

Abbreviations: EBRT, external beam radiation therapy; RAI, radioactive iodine therapy; Total plus neck, total plus any type of neck or mediastinal lymph node dissection.

aAccording to the classification system by DeGroot et al.20

**COMMENT**

Most thyroid cancer cases have a favorable disease outcome, and most patients enjoy complete remission after their initial treatment. However, a significant proportion of patients experiences mortality and morbidity from the disease. As a result, there has been a great deal of research interest in identifying factors that may cause patients to have poor prognoses from thyroid cancer. Many
such factors have been described in prognostic risk stratification systems such as the AMES [age, metastases, extent, and size], AGES [age, grade, extent, and size], and MACIS [metastases, age, completeness of resection, invasion, and size] methods.3

To our knowledge, race/ethnicity has never been described as a factor that may affect thyroid cancer prognosis. Despite reports of racial/ethnic disparities in cancer outcomes for breast, endometrial, and other cancers,1,2,21,22 this issue has not been explored in any detail for thyroid cancer. Several studies12-14,23 have identified racial/ethnic populations with an increased incidence of thyroid cancer. Filipinos have an especially high risk of developing thyroid malignant neoplasms, which independent studies12,14-19 have estimated to be several-fold above that of the general population.

Given the increased incidence of thyroid cancer among Filipinos, this population may also be at increased risk of negative thyroid cancer outcomes such as death or recurrence and may require more aggressive treatment. With this in mind, it was the objective of the present study to evaluate the outcomes of Filipino patients having thyroid cancer with respect to the rate of death from disease, the presence of thyroid cancer recurrence, and the time to recurrence to identify whether this racial/ethnic group was at higher risk of a poor prognosis.

Using a retrospective medical record review of patients treated for thyroid cancer at a tertiary referral center, this study found no significant difference between Filipino patients and non-Filipino patients with respect to the rate of death from disease and the time to recurrence (P = .16 and P = .98, respectively). However, Filipino patients experience a significantly increased rate of thyroid cancer recurrence (25.0% vs 9.5%) compared with non-Filipino patients (OR, 3.20; 95% CI, 1.23-7.49; P = .004). This increased risk of thyroid cancer recurrence for Filipino patients persists when confounding factors are controlled for on multivariate analysis (OR, 6.99; 95% CI, 2.31-21.07; P < .001). These findings are noteworthy because they identify Filipino patients as a high-risk group with respect to thyroid cancer outcomes and provide the first evidence to date of race/ethnicity as a possible prognostic factor in thyroid cancer.

The limitations of this study include its limited sample size and the inherent weaknesses associated with retrospective medical record reviews. The study cohort consisted of all cases referred to one of us (J.L.F.) by the study’s senior endocrinologist (P.G.W.), with no detectable selection bias based on patient race/ethnicity. Only 36 Filipino patients with thyroid cancer met the study’s selection criteria, which included a minimum 1.0-cm tumor size and a minimum 5-year follow-up period. These criteria were chosen to allow for an adequate period for assessing the presence of thyroid cancer recurrence and the rate of death from disease and to select only clinically relevant tumors. The Filipino and non-Filipino groups were similar, with only marginally significant differences in age and tumor pathologic findings that are not thought to have affected the overall findings. Although patient age has been implicated as a prognostic factor in thyroid cancer,4 the small difference in age between our study groups is likely explained by the higher percentage of patients 60 years or older in the non-Filipino group. Therefore, any effect of this factor would likely have led to an underestimate of the increased thyroid cancer recurrence risk among Filipino patients. The small statistical difference in tumor pathologic findings is likely accounted for by the small differences in the less common histologic subtypes combined with the small sample size of the Filipino group. All cases of thyroid cancer recurrence in the Filipino group occurred among patients with well-differentiated thyroid carcinoma, arguing against the effect of tumor pathologic findings as a factor that affected the overall recurrence results. Moreover, when multivariate analysis was performed with exclusion of the aggressive tumor varieties (insular, anaplastic, and medullary), the results were almost identical, further validating our conclusions.

Several theories related to environmental exposure have been proposed to explain the increased incidence of thyroid cancer among Filipinos and could relate to the elevated thyroid cancer recurrence rate in this population. Among them, high-iodine diet from fish and other seafood,16 low dietary consumption of carotenoids and isoflavones,18 and exposure to a possible carcinogenic agent in volcanic lava12 have been cited. No clear consensus exists to elucidate the epidemiologic observations. There is no literature regarding any pathogenesis that might explain our observation of increased thyroid cancer recurrence among Filipino patients. This is an area that warrants further investigation. Future studies should focus on delineating the etiology of these increased thyroid cancer incidence and recurrence rates by comparing the effects of such environmental factors on Filipino-born and North American–born Filipino patients. Another topic for future study could be to explore the possible association between genes such as MAPK, BRAF, RAS, and RET that are involved in the pathogenesis of thyroid malignant neoplasms24 and the pattern of thyroid cancer incidence and recurrence among the Filipino population.

The results of our study suggest that clinicians should have a heightened clinical suspicion for regional metastasis among Filipino patients having thyroid cancer and that these patients require closer follow-up than other patients with similar disease characteristics. Based on previous studies of the increased thyroid cancer incidence among the Filipino population12,14,19 and the rate of cancer diagnosis in Filipino patients with thyroid nodules,16 the current standard of treatment at Mount Sinai Hospital for Filipino patients with palpable (≥1.0 cm) thyroid nodules is total thyroidectomy, regardless of fine-needle aspirate biopsy findings. In our study, only 9 Filipino patients experienced thyroid cancer recurrence; therefore, no definitive conclusions can be made regarding patterns of failure. Nevertheless, most patients had regional failure; in light of these findings, we suggest that Filipino patients should be managed in a manner similar to that of patients deemed to have a high risk of thyroid cancer recurrence according to American Thyroid Association criteria.23 These guidelines include preoperative computed tomography to investigate any subclinical lymphadenopathy and more frequent follow-up by imaging and serum thyroglobulin measurement.
In conclusion, we present herein the first evidence to date of an association between patient race/ethnicity and thyroid cancer prognosis. Filipino patients experience a significantly higher rate of thyroid cancer recurrence than similar patients of other races/ethnicities but are not at increased risk of a shorter time to recurrence or death from disease. Based on these findings, a more aggressive management plan may be appropriate for this patient population.

Submitted for Publication: April 28, 2009; final revision received April 25, 2009; accepted September 22, 2009.

Correspondence: Jeremy L. Freeman, MD, FRCSC, Department of Otolaryngology–Head and Neck Surgery, Mount Sinai Hospital, 600 University Ave, Room 401, Toronto, ON M5G 1X5, Canada (jfreeman@mssinai.on.ca).

Author Contributions: Mr Kus and Dr Freeman had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kus, Wallfish, and Freeman. Acquisition of data: Kus, Shah, and Eski. Analysis and interpretation of data: Kus. Drafting of the manuscript: Kus, Shah, and Eski. Critical revision of the manuscript for important intellectual content: Kus, Wallfish, and Freeman. Statistical analysis: Shah. Obtained funding: Freeman. Administrative, technical, and material support: Eski. Study supervision: Wallfish and Freeman.

Financial Disclosure: None reported.

Funding/Support: This study was supported by grants from the Mount Sinai Hospital Department of Medicine Research Fund, The Mount Sinai Hospital Foundation of Toronto, and the Joseph and Mildred Sonshine Family (Dr Wallfish) and from Temmy Latner and Dynacare (Dr Freeman).

Additional Contributions: Temmy Latner and Dynacare provided support to the Department of Otolaryngology–Head and Neck Surgery.

REFERENCES